REMARKS

In response to the Office Action mailed October 27, 2008, Applicant respectfully requests reconsideration. Claims 13, 17-22, 25-27 and 54-56 were previously pending in this application and remain pending for examination, with claim 13 being independent. No claims have been amended and no new matter has been added.

Applicant notes that the Office Action indicates on page 6 that it is a final Office Action, but this appears to be an error since the Office Action Summary page indicates that the Office Action is non-final, and the rejection of the claims as obvious is not properly made final.

Rejections Under 35 U.S.C. § 102

The Examiner rejected claim 20 under 35 U.S.C. § 102(a) as allegedly anticipated by Fire et al. (WO 99/32619 A1, the "Fire PCT application"). The Examiner also rejected claim 20 under 35 U.S.C. § 102(e) as allegedly anticipated by Fire et al. (US 6,506,559, the "Fire US patent"). Applicant respectfully requests reconsideration and withdrawal of both rejections.

The Examiner withdrew the prior anticipation rejections of the claims except for claim 20, which remains rejected over the Fire PCT application and the Fire US patent. Applicant respectfully disagrees with the Examiner that these rejections are proper. Claim 20 depends from claim 19, which in turn depends from claim 13. If claims 13 and 19 are considered novel over the Fire patent references as must be based on the withdrawal of the rejections of these claims as anticipated, then claim 20, which includes all of the features of claims 13 and 19, cannot be considered to be anticipated by the Fire PCT application or the Fire US patent.

Accordingly, Applicant respectfully requests that the rejection of claim 20 as anticipated by the Fire PCT application and the Fire US patent be withdrawn.

Rejections Under 35 U.S.C. § 103

The Examiner rejected claims 13, 17-22, 25-27 and 54-56 under 35 U.S.C. § 103(a) as allegedly unpatentable over Fire et al. (U.S. Patent No. 6,506,559, the "Fire US patent") in view of Zdinak et al (Journal of Cellular Biochemistry, 1997, 67:143-153), Talkad et al. (Journal of Bacteriology, 1978, 135:528-541) and Noren et al. (U.S. Patent No. 5,691,140). Applicant respectfully requests reconsideration.

The Examiner rejected the claims based on a four reference combination that includes two new references: the Noren patent and the Zdinak reference.

Dr. Erwin Sablon states that the Noren et al. patent describes multipurpose cloning vectors for *in vitro* generation of high specific-activity RNA probes. (See Sablon Declaration, ¶7). These vectors contain a multiple cloning site flanked by two phage RNA polymerase promoters positioned to express either strand of a DNA molecule inserted in the multiple cloning site. (See Sablon Declaration, ¶7). These flanking promoters can be the same or different, such as two T7 promoters or a T7 promoter at one side and a SP6 promoter at the other side. (See Sablon Declaration, ¶7). This agrees with the description in the Noren et al. patent (see, for example, column 2, lines 14-28 and column 8, line 64 to column 9, line 25).

The vectors described in the Noren et al. patent are used to generate either sense or antisense transcripts from the same vector *in vitro*, using the appropriate phage RNA polymerase. (See Sablon Declaration, ¶8). As stated by Dr. Sablon, in order to generate highly specific RNA probes, it is crucial that only one strand becomes transcribed. (See Sablon Declaration, ¶9). Transcription of only one strand of the vector can be accomplished by one of two methods. First, the vector can be linearized with a particular restriction endonuclease that cuts between the insert and one of the flanking promoters in order to ensure transcription of only one strand. (See Sablon Declaration, ¶9). This method is typically used when both flanking promoters are of the same type. (See Sablon Declaration, ¶9). Second, only one promoter-specific phage RNA polymerase can be used in the *in*

vitro transcription reaction. (See Sablon Declaration, ¶9). This method is typically used when the two flanking promoters are of different origin. (See Sablon Declaration, ¶9).

In contrast to the vectors recited in the claimed invention, the vectors described in the Noren et al. patent "were clearly not intended to simultaneously produce transcripts from both directions." (See Sablon Declaration, ¶10). Instead, the application describes, and the claims recite, the use of bidirectional expression vectors for *in vivo* generation in *E. coli* of double stranded RNA. (See Sablon Declaration, ¶11). Dr. Sablon states that such a use would not have been suggested to the person of ordinary skill in the art by the Noren et al. patent for the reasons stated above. (See Sablon Declaration, ¶11). Moreover, according to Dr. Sablon, bidirectional expression vectors that have opposite RNA polymerase promoters have been well known to and universally used by molecular biologists since the mid 1980s. (See Sablon Declaration, ¶11). Notwithstanding the prior knowledge of the vectors in the art, Dr. Sablon states that the use of this type of vector even for *in vitro* production of both strands of double stranded (ds) RNA simultaneously, let alone *in vivo* production of dsRNA in a microorganism, was not even contemplated by any molecular biologist at that time, and in fact was not until the present invention in the late 1990s. (See Sablon Declaration, ¶11).

Therefore, the disclosure of the Noren et al. patent differs from the claimed invention in that it teaches *in vitro* and unidirectional transcription only, and does not describe bidirectional transcription that would produce double stranded RNA.

The Zdinak reference allegedly describes that one can express a transgene in *C. elegans* by feeding it with *E. coli* expressing the transgene. On page 4 of the Office Action, the Examiner stated that: "Zdinak et al. teach that one can express a transgene in *C. elegans* by feeding *E. coli* that expresses the transgene. In fact, they teach that *E. coli* has been the usual food source for experimental *C. elegans* in the art." On page 6 of the Office Action, the Examiner stated that "feeding *E. coli* to *C. elegans* was an art-recognized method for expressing transgenes in the *C. elegans*."

Dr. Sablon disagrees with these statements of the Examiner and furthermore disagrees with the argument "that one can express a transgene in *C. elegans* by feeding *E. coli* that express the transgene" can be concluded from the Zdinak et al. article. (See Sablon Declaration, ¶13).

According to Dr. Sablon, the Zdinak et al. article describes the effect of starvation on the fate of a transgenic muscle cell expressed lacZ fusion protein in the nematode *C. elegans* by withdrawal of the food source, *E. coli*. (See Sablon Declaration, ¶14). Zdinak et al. used the *Caenorhabditis elegans* strain PD55 in all of the experiments (see the "MATERIALS AND METHODS" section beginning on page 144 and the "RESULTS AND DISCUSSION" section beginning on page 147. (See Sablon Declaration, ¶14). As indicated in the references cited in the Zdinak paper (Fire and Waterston, 1992. EMBO J 8:3419-3428; Okkema et al., 1993. Genetics 135:385-404), copies of which are enclosed herewith, *C. elegans* strain PD55 contains an integrated transgene, ccIs55. (See Sablon Declaration, ¶14). This *C. elegans* strain was generated through microinjection and not by gene transfer from fed *E. coli* cells. (See Sablon Declaration, ¶14).

Therefore, according to Dr. Sablon, the Zdinak et al. article does not give any evidence that can one express a transgene in *C. elegans* by feeding *E. coli* that express the transgene, let alone expressing in *C. elegans* double stranded RNA from an expression vector in *E. coli* or other microorganism. (See Sablon Declaration, ¶15).

Therefore, Applicant submits that the combination of references cited by the Examiner fails to teach or suggest to the skilled person all of the elements of the claimed invention.

Moreover, according to Dr. Sablon, none of the documents cited by the Examiner teach or suggest (alone or in combination) that one can express a double stranded RNA in a microorganism. (See Sablon Declaration, ¶16). Nor do the documents cited by the Examiner teach or suggest that when such a microorganism is ingested by *C. elegans*, the double stranded RNA is "liberated" from the microorganism and that the double stranded RNA has a biological effect in the cells of the *C.*

elegans, in particular the effect recited in the claims, down-regulating the expression of a gene of interest in *C. elegans*. (See Sablon Declaration, ¶16).

Dr. Sablon states that his opinion is that a person of ordinary skill in the art would not have had a reasonable expectation of success of practicing the claimed invention based on the combination of references cited by the Examiner. (See Sablon Declaration, ¶17). More specifically, Dr. Sablon stated that a person of ordinary skill in the art would not have had a reasonable expectation of success based on the combination of references cited by the Examiner of using the type of vectors known in the art to express double stranded RNA inside a microorganism, feeding such a microorganism that expresses the double stranded RNA "inside" its cell wall to *C. elegans*, and exerting an effect, from the inner content of the bacterium towards the cell cytoplasm of *C. elegans* cells. (See Sablon Declaration, ¶17).

Therefore, Applicant submits that the combination of references cited by the Examiner fails to provide a person of ordinary skill in the art with a reasonable expectation of success of practicing the claimed invention, as required for a finding that the claims are obvious.

Accordingly, Applicant respectfully requests that the rejection of claims 13, 17-22, 25-27 and 54-56 under 35 U.S.C. 103 be withdrawn.

CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below to discuss any outstanding issues relating to the allowability of the application.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, the Director is hereby authorized to charge any deficiency or credit any overpayment in the fees filed, asserted to be filed or which should have been filed herewith to our Deposit Account No. 23/2825, under Docket No. D0590.70011US00.

Dated: April 21, 2009

Respectfully submitted,

By: /John R. Van Amsterdam/
John R. Van Amsterdam
Registration No.: 40,212
WOLF, GREENFIELD & SACKS, P.C.
Federal Reserve Plaza
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
617.646.8000

x04/27/09x